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PAPER NUMBER

22

1211

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This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

### OFFICE ACTION SUMMARY

Responsive to communication(s) filed on 12-16-97

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

- 26
- Claim(s) 1-8, 10, 28, 29, 31 and 37 is/are pending in the application.  
Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- Claim(s) \_\_\_\_\_ is/are allowed.
- Claim(s) 1, 5, 26, 28, 29, 31 and 37 is/are rejected.
- Claim(s) 2-4, 6-8, 10 is/are objected to.
- Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.
- The specification is objected to by the Examiner.
- The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

- All  Some\*  None of the CERTIFIED copies of the priority documents have been
- received.
- received in Application No. (Series Code/Serial Number) \_\_\_\_\_
- received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- Notice of Reference Cited, PTO-892
- Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_
- Interview Summary, PTO-413
- Notice of Draftsperson's Patent Drawing Review, PTO-948
- Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES-

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***Transitional After Final Practice***

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 12-16-97 has been entered.

***Response to Amendment***

The amendment filed 12-16-97 has been entered. Claims 1-8, 10, 26 and 31 have been amended. Claims 9, 11-25, 27, 30 and 32-36 have been canceled. New claim 37 has been added.

***Claim Rejections - 35 USC § 112***

Claims 5, 29 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is vague because the "X" variable is not defined. Also, variables "R<sup>5</sup>" and "R<sup>6</sup>" are defined, but are not shown in the claimed formula and therefore are confusing. It is suggested that variable "X" is defined in the claim and the recitations of "R<sup>5</sup>" and "R<sup>6</sup>" are deleted.

Claim 29 is indefinite because it is dependent upon a canceled base claim (i.e., claim 27).

Claim 37 is vague because none of the variables (i.e., R, R', p, n, m) are not defined.

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***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 26, 28, 29, 31 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fritzberg, USP 4,965,392 (or USP 5,091,514).

The claims of the instant invention appear to be directed toward a monoamine, diamide, thiol containing metal chelator covalently linked to a targeting moiety.

Fritzberg '392 and '514 discloses compositions used as reagents for preparing radiopharmaceutical agents comprising a chelating agent (radiometal binding moiety) such as a monoamine, diamide, thiol-containing chelator linked to a targeting moiety. Fritzberg discloses chelating agents having the structure in column 3 wherein X is, independently, H<sub>2</sub> or O. This formula may be substituted wherein two of the X substituents are O, and the remaining X is H<sub>2</sub>, thus the compound would be a monoamine, diamide, thiol-containing chelator similar to those of the instant claims, i.e., instant claim 37. Fritzberg also discloses chelators wherein Z is -HN2 and having 0-3 amide groups. Any of the chelators (even the so-called "triamides") would read on instant claim 1, because they would have at least two amides, at least one amine and a thiol. Note, additional amides groups, etc. (i.e., in the triamides disclosed by Fritzberg) of the prior art would not exclude such chelators from the instantly claimed "monoamine, diamide, thiol

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containing chelators," just as the additional alkylene groups, etc. do not exclude the chelators of claim 2 from those of claim 1. Additionally, Fritzberg '392 and '514 disclose that the chelating agent may be conjugated to polypeptides, antibodies, hormones, etc. as a specific binding moiety, see abstract and column 4.

Although Fritzberg '392 and '514 may not specifically disclose all of the same monoamine, diamide, thiol-containing metal chelating agents which are linked to the same targeting moieties of the present claims, it would have been obvious to one of ordinary skill in the art to synthesize such monoamine, diamide, thiol-containing metal chelator covalently linked to a targeting moiety because Fritzberg '392 and '514 disclose formulae which may be substituted to yield various ligands which would be encompassed by a monoamine, diamide, thiol-containing metal chelating agents, which provide the advantage of *in vivo* targeting of a radiopharmaceutical for treatment or diagnosis.

#### *Response to Arguments*

Applicant's arguments filed 12-16-97 have been fully considered but they are not persuasive.

Applicant asserts that the 37 USC 1.132 declaration filed by an expert in the field on 12-16-97 overcomes the obviousness rejection over Fritzberg because Fritzberg disclosure lacks disclosure of a method of making a monoamine, diamide, thiol-containing metal chelator. The

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remaining statements in the declaration appear to assert that the Fritzberg reference teaches triamide thiol chelators but does not teach monoamine, diamide thiol chelators or provide a teaching that would provide a reasonable expectation of success in making and using monoamine, diamide thiol chelators.

The declaration under 37 CFR 1.132 filed 12-16-97 is insufficient to overcome the rejection of claims 1-10, 26 and 31 based upon Fritzberg as set forth in the last Office action because of the following reasons.

Applicant's assertion is not persuasive because, first, these assertions are not found persuasive because Fritzberg teaches chelators of the formula shown in column 3, wherein X may be H<sub>2</sub> or =O. Substituting one of the X's as H<sub>2</sub> and the others as =O, would yield a monoamine, diamide thiol chelator. Although Fritzberg may not exemplify a monoamine, diamide thiol chelator (as defined by applicant) such chelators are clearly taught in the specification of Fritzberg and would be enabled by one of ordinary skill in the art by routine chemistry, e.g., reducing a carbonyl group of a precursor of the chelating agent (e.g., of an amino acid) to an H<sub>2</sub>. A reference is presumed operable until applicant provides facts rebutting the presumption of operability. *In re Sasse*, 207 USPQ 107 (CCPA 1980). Therefore, applicant must provide evidence showing that a process for making was not known at the time of the invention. However, the fact that an author of a publication did not attempt to make the compound disclosed, without more, will not overcome a rejection based on that publication. *In re Donohue*, 226 USPQ 619 (Fed. Cir. 1985). Also, a reference as a whole must be considered, e.g., the

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specification teaches more than its working examples. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 10 USPQ2d 1843 (Fed. Cir. 1989).

Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 169 USPQ 423 (CCPA 1971).

Secondly, the chelators taught by Fritzberg which are referred to by applicant as “triamide thiol chelators” would be encompassed by the claimed recitation of “monoamine, diamide thiol chelators” given the broadest reasonable interpretation. Fritzberg teaches chelators having at least two amides (diamide), at least one amine (see Z is -NH<sub>2</sub>, e.g., monoamine) and a thiol. Thus, the so-called “triamide chelators” disclosed by Fritzberg would be encompassed by the recitation of claim 1, since they contain the same groups as recited in the claim, while additional groups would not be capable of excluding such chelators, (note: applicant’s chelators also contain other groups, alkylene groups, side chains, etc.). Office personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. See, e.g., *In re Zletz*, 893 F.2d 319, 321 - 22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (“During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow . . . . The reason is simply that during patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed . . . . An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative

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process."). Since the instant recitation of "monoamine, diamide, thiol containing chelators" does not appear to exclude other chemical moieties, it would read upon any chelator having at least one amine, at least two amides and a thiol. The chelators disclosed by Fritzberg clearly encompass such chelators.

The Applicant's response in the amendment filed on 12-16-97 to the rejection of claims 2-10 made by the Examiner under 35 U.S.C. § 103(a) over Fritzberg, fully meets the deficiencies encompassed by said rejection. Therefore, said rejection is hereby withdrawn.

The Applicant's response in the amendment filed on 12-16-97 to the rejection of claims 1-10, 26 and 31 made by the Examiner under 35 U.S.C. § 103(a) over Rhodes, fully meets the deficiencies encompassed by said rejection. Therefore, said rejection is hereby withdrawn.

*Allowable Subject Matter*

Claims 2-4, 6-8 and 10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The instant claims appear to be free of the art of record because the prior art does not teach or suggest chelates of the formula shown in claim 2, such as, chelates having amide

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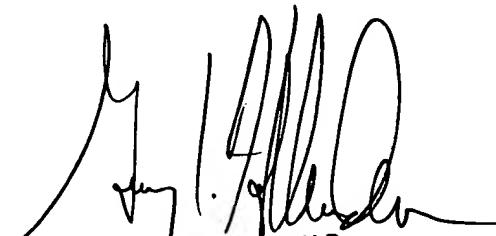
substitutions at the positions of the chelator shown in claim 2. It would not have been obvious to one of ordinary skill in the art to modify the chelators disclosed by Fritzberg to yield the instantly claimed compounds because the formula disclosed by Fritzberg cannot be substituted to yield chelators of the instantly claimed formula and differs substantially from the formula of instant claim 2, as set forth in applicant's arguments and paragraph 4 of the declaration, filed 12-16-97. Also, claim 5 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112 set forth in this Office action and to include all of the limitations of the base claim and any intervening claims, (i.e., claim 2).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Michael Hartley whose telephone number is (703) 308-4411. The examiner can usually be reached on Teusday through Friday from 7:30 a.m. to 5:00 p.m. in the eastern time zone and on alternate Mondays. The facsimile numbers for group 1200 are (703) 308-4556 or (703) 305-3592.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Kight, III, SPE 1211 can be reached on (703) 308-0204.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

M. Hartley  
Date: 2-2-98



GARY E. HOLLINDEN, PH.D.  
PRIMARY EXAMINER  
GROUP 1200